Roche

March 16, 2005

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0355: Comments following February 14-16, 2005 FDA/DIA Meeting on Follow-on Protein Products.

Dear Sir or Madam:

Hoffmann-La Roche, Inc. (Roche) is pleased to have an opportunity to provide further comments on critical issues relating to the development of follow-on biologics (FOBs) in response to the Public Workshop on Scientific Considerations in the Development of Follow-on Protein Products held February 14-16, 2005. The Roche participants at the meeting found it to be an excellent forum for open communication of critical issues among regulators and the industry stakeholders, and we thank the organizing committee for their excellent work.

The presentations from speakers and working group discussions at the meeting, however, made it clear that there are a number of points upon which the innovator and FOB companies fundamentally disagree, and it is critical that FDA carefully consider these before any draft regulatory guidance is prepared and released by the Agency. In the interest of sharing our global experience in development of novel biologic products, Roche believes there is a need for further clarification of the following points:

- **Comparability vs. Similarity**: : There are critical differences between the ability to demonstrate the impact of incremental changes to a process where the full product history is known (comparability) and the impact of a new process including new cell line on safety and efficacy (similarity). When a manufacturer is able to evaluate, through analytical and functional assays, the change of a single parameter, this can be related to an historical database facilitating the overall impact. A similarity protocol is based on an entirely different premise where the product is derived from a new process.

- **Importance of Clinical Data to Support Any Unique Protein Product (innovator or FOB)**: There was considerable discussion at the meeting of the extent to which a clinical program needs to be part of the development of any potential FOB. Roche wants to reaffirm the importance of establishing a robust human clinical database, pre-approval, for any new biologic, whether a new product, or FOB. Post-approval, a unique system is needed for any and all biologic products, for each separate indication and route of

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administration. When registries are appropriate, it is critical to track each new biologic (FOB or innovator) separately through a unique coding number and independent, but cross-traceable registry. Indeed, we believe separate nomenclature should be established for any FOB product to further protect patient safety.

- **Critical Legal Issues re Statutory Protection for Intellectual Property and the Establishment of Reference Standards for Review of Sameness**: It is critical that development of FOB guidelines, including the reference to the necessary clinical data and other proprietary information developed by the innovator, accurately reflect the carefully constructed statutory framework.

Our detailed comments on these three issues are provided below.

Comparability vs. Similarity

During the recent discussions concerning comparison of a follow-on biological product (FOB) to the approved product there have been many references to the ability of the manufacturer of a follow-on product to use state-of-art analytical technology to demonstrate comparability of the new FOB to the approved product. Roche believes that references to comparability in this situation are inappropriate and may be misleading. It is critical when discussing manufacturing changes to an innovator product or FOBs to make a clear distinction between comparability and similarity assessments. Roche recommends that specific terminology be defined to distinguish comparability of pre- and post-change materials from within an established process versus similarity of two products produced by different manufacturers/sources/processes. Comparability as described in current ICH and FDA guidances is well defined for assessment of changes within a process. The requirements and conditions for similarity are not clearly defined by guidance and criteria need to be established in order to compare products from different manufacturers and processes. We believe that in all cases, similarity assessments for an FOB must include at a minimum PK and clinical data, as well as analytical information.

At Roche, changes to any biologic manufacturing process are usually implemented incrementally so that impact can be assessed immediately following the point of the change as well as on the finished drug substance and drug product. The analytical component of a comparability assessment typically includes comparative evaluation of in-process controls, release data, extended characterization and functional assay(s) for drug substance and often drug product. Acceptance criteria are based on approved specifications and trend analysis from the historical performance of the established process. For major changes, pre-clinical and clinical data may also be required to demonstrate comparability. One example from Roche's experience concerned a non-glycosylated protein in Phase III clinical trials where it was necessary to change the promoter of the production strain. In this case, analytical comparability was demonstrated including full comparison of the entire manufacturing process pre- and post change, comparative in-process control testing and drug substance release testing. Additionally, a pharmacokinetic bioequivalence study in dogs demonstrated comparability of the drug substances pre- and post change. After discussion of the change and the available comparability data with FDA and EU authorities, the design of the Phase III trial was adapted to allow a distinct evaluation of the two

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materials in patient subgroups such that patients receiving the new material were defined and could be traced back.

Manufacturers of FOBs implement new and substantially different manufacturing processes to develop their product. In this situation, many critical parameters (e.g., cell line, fermentation and purification processes, and formulation) will likely be different from those used by an innovator and significantly affect the biological properties of the biologic product, even if the final product specifications remain unchanged. Even in the best of circumstances, the FOB manufacturer is limited in the analytical component of the evaluation because it is not possible to perform comparative analyses for in-process controls on the drug substance, or to utilize process trend data. It is also likely that many impurities cannot be adequately assessed based on analysis of the finished drug product alone. Analytical comparability for this type of comparison is inadequate to establish similarity between the reference approved product and a follow-on version. Because similarity assessment cannot be performed at the level of the manufacturing process for different manufacturers, a similarity assessment must include appropriate pre-clinical and clinical data in addition to the available comparative analytical data for the drug products in order to fully assess the impact of the differences in the process and product on quality, safety and efficacy.

Based on years of experience with the established product's manufacturing process and performance in the clinic and real world setting an innovator may decide to add preclinical, PK and clinical analysis to assess the impact of critical or multiple changes on a drug product. For an FOB, without this experience and with a different manufacturing process in place this type of additional information should not be optional. Any FOB product should be required to be supported by adequate clinical data prior to receiving marketing authorization. For multiple major changes to the drug substance and product, a single clinical trial with post-marketing surveillance is insufficient to demonstrate the similarity of a follow-on product to the safety and efficacy of the established marketed product. There is and should be no substitute for pre-approval PK and clinical information as part of a similarity assessment for an FOB.

The importance of clinical data and safety tracking – pre and post-approval

In addition to the comparability issues raised above, Roche would like to further emphasize the need to establish safety of an FOB, especially pre-approval. At the February Workshop, there was a significant discussion on the need for PK/PD and clinical studies in conjunction with adequate characterization to support any product interchangeability. It is the position of the FOB manufacturers that minimal PK data, but not clinical data, may, on a case-by-case basis, be needed for approval of an FOB, but that pre-marketing clinical studies should not be required, as post-marketing safety studies will suffice.

Dr. Mark Rogge from ZymoGenetics represented the innovator company position and discussed the importance of both PK and PD studies to support physical and biologic characterization and examples of how plasma and tissue distribution may vary with minor differences in products. Performing PK/PD studies is a general rule throughout drug development for innovators and should not be optional or minimal for FOBs. Although PK/PD studies can support safety and efficacy, and are used by the innovator companies to do so, they do not necessarily translate into

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confirmatory evidence for clinical outcomes. It is critical in terms of establishing the safety profile of FOBs that both plasma and tissue distribution for a product be studied and further that clinical experience be obtained, pre-marketing authorization.

While it was widely agreed among FOB and innovator manufacturers that immunological as well as other safety concerns need to be assessed clinically for all biologics, the possibilities that post-marketing rather than pre-marketing data can be used to support safety is a point of disagreement between the FOB and innovator companies. We at Roche want to restate our strong belief that performing adequate assessments of safety of a FOB is not and should not be considered "reinventing the wheel" but rather adhering to good scientific and medical practice. It should also be reemphasized that there is a need to perform separate clinical studies for separate indications for FOBs as for innovator drugs, as there is no way to adequately assure safety of an innovator or an FOB product, cross-indication, without clinical data.

In terms of detection of emerging safety issues post-marketing, it is critical that FOB and innovator product safety can be followed and tracked separately post-marketing, with a unique name or code (perhaps a unique INN number), to assure proper identification of any specific problem products. Based on the previous industry experience, it is clear that looking at the safety of a class of biologics and their follow-ons is not sufficient, thus a system for unique product tracking must be established.

For most products, routine pharmacovigilance is sufficient for post-marketing risk assessment. However, in certain limited instances, unusual safety signals may become evident either before or after that could suggest that consideration by the sponsor of enhanced pharmacovigilance efforts or a pharmacovigilance plan may be appropriate. A pharmacovigilance plan could include the creation of registries and if the innovator product has a registry, we urge FDA to enforce that the FOB establish a separate, traceable, and cross-referenced registry. A process should be implemented such that if an innovator biologic has established a registry, the FOB manufacturer's registry must be similar in detail and quality to the innovator registry. In addition, there must be a system established such that the unique FOB registry can be cross-referenced to the innovator's tracking system to assure no overall trends in safety are overlooked. If potential safety differences emerge, the FDA will need to address these in terms of potential labeling differences. Detailed recommendations establishing such a unique post-marketing surveillance system should be in place prior to any FOB approvals and should be a critical point in FDA's guidance to sponsors on this subject.

Legal Issues

Roche also would like to emphasize that it is necessary to recognize that the scientific issues noted above cannot be separated from the legal framework that would need to be established for FDA approval of follow-on biologics. The numerous concerns regarding the safety and effectiveness of follow-on biologic products cannot be resolved in the absence of a clear understanding about what information FDA may use or rely upon from an innovator's application in its review of subsequent applications. This is especially critical considering that current science is inadequate to ensure the safety and effectiveness of follow-on products that

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would rely substantially upon the analytical data from an innovator's product when the follow-on product is developed by a different manufacturing process. As noted above, such reliance is not possible because follow-on biologics are difficult to characterize and there currently is no scientifically valid methodology for establishing the "sameness" of two products. Therefore, extensive safety and clinical information would be needed in order for the Agency to make valid comparisons between the innovator and subsequent products. In the absence of this extensive safety and effectiveness information, the Agency would only be able to perform the rigorous scientific evaluation needed to assure "sameness" by relying upon the information submitted by the manufacturer of the innovator product. However, the information submitted by the innovator is trade secret and commercial confidential, and under current law, the use of this information by FDA reviewers to assess a product other than that of the innovator is clearly prohibited. For the reasons noted above, an abbreviated pathway similar to that established for small molecules is not feasible in the case of follow-on biologics.

Although the primary purpose of the February Public Workshop was to address the scientific issues associated with FOBs, Roche believes that it is important to consider the serious legal concerns that these proposed products raise. As discussed in other comments submitted to the Docket, the existing statutory authorities, whether under Section 505(b) 2 of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, do not permit FDA to approve FOBs based upon prior findings of safety and efficacy for innovator products. Innovator biologic companies invest tremendous resources to develop the complex processes and data necessary to support product manufacturing and approval. Any FDA reliance on such proprietary innovator data in the review of an FOB product would risk violating the above-referenced statutory framework and presents serious constitutional issues. It is thus critical that FDA carefully consider, in a public manner, the legal constraints on any further action relating to FOB approvals, as well as the potential impact of any such approvals on future innovator biologic product development.

In conclusion, Roche appreciates the opportunity to add our scientific expertise and insight into the complex discussion of the scientific expectations for bringing a follow-on-biologic to market. We believe that the February workshop was an excellent opportunity to exchange information on the significant challenges that must be considered as discussions continue on this topic. If you have any specific questions about the content of this response, please contact the undersigned.

Respectfully submitted,

for

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